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| EXAMINER | |
|---|---|
| WESSENDORF, TERESA D | |
| **ART UNIT** | **PAPER NUMBER** |
| 1639 | |

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/057,810 | LI ET AL. | |
| | Examiner | Art Unit | |
| | T. D. Wessendorf | 1639 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11/22/04 and 6/30/04*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-19,21-31 and 47-50* is/are pending in the application.

4a) Of the above claim(s) *25-28 and 47-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,21-24 and 29-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

***Election/Restrictions***

***Response to Arguments***

Applicants argue that pursuant 37 C.F.R. 1.145, if, after an office action on an application, the applicant presents claims directed to an invention distinct from and independent of the invention previously claimed, the applicant will be required to restrict the claims to the invention previously claimed if the amendment is entered, subject to reconsideration and review as provided in 1.143 and 1.144. Since claims 25-28 and 47-50 are dependent from claim 1 that specifies the invention Applicants elected in the Amendment filed in response to the Examiner's Restriction Requirement, these claims are not the type of claims required by 37 C.F.R. 1.145 to be reconsidered and reviewed under 37 C.F.R. 1.143 and 1.144.

In response, claims 47-50, as applicants recognized, are drawn to independent and distinct invention, albeit dependent on claim 1. This will impose undue burden on the already or originally examined subject matter. These claims present limitations not originally presented. The withdrawal of the newly added claims from consideration is in essence a restriction as argued by applicants, albeit under 37 CFR 1.142(b) not under 37 CFR 1.143 and 1.144. See MPEP 821.03. As stated in the last Office action, claims 47-50 relate to the

identifying the type of the cell sample which will encompass different process step. Claims 25-28 have been withdrawn since these claims recite additional steps not encompassed in the elected method.

***Status of Claims***

Claims 1-19, 21-31 and 47-50 are pending in the application.

Claims 20 and 32-46 have been cancelled.

Claims 25-28 and 47-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 1-19, 21-24 and 29-31 are under examination.

***Withdrawn objections and rejections***

In view of the amendments to the specification, the objection is withdrawn. Also, in view of applicants' arguments the Obviousness double patenting rejections are withdrawn.

***Claim Rejections - 35 USC § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19, 21-24 and 29-31, as amended, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons advanced in the last Office action.

***Response to Arguments***

Applicants direct the Examiner's attention to pages 12-15, a section under "DETAILED DESCRIPTION OF THE INVENTION" and Figures IA, IB, and 2. It is argued that Figure 2 shows examples of the cis element (e.g., SEQ ID N0: 1) and examples of the reporter sequence (e.g., SEQ ID NO: 31) corresponding to the cis element listed in the column to its left side. Upon binding of the transcription factor to the cis element and activation of transcription, the cis element and its accompanying reporter sequence are transcribed. Because each cis element is tagged with a different reporter sequence, identification of the reporter sequence will lead to identification of the activated transcription factor that binds to the cis element. Page 12, lines 22-31. Figure IA illustrates an embodiment of the invention in which mRNA

of the transcribed reporter sequences in the construct is isolated and reverse transcribed into cDNA which is then characterized. Characterization of the cDNA translates into the identification of the cis element, which in turn results in identification of the corresponding transcription factor. Page 14, lines 11-16. The specification further teaches how to construct the cis element-reporter construct on pages 15-19, and how to detect activated transcription factor on pages 19-28.
In response a review of the cited sections e.g. pages 12-15 and Figs. IA, B and 2 reveal a general statement of said method. As stated by applicant the method is drawn to identifying a transcription factor. But not a single transcription factor has been identified from a library that contains millions of compounds. Applicants' arguments simply repeat the general statements in the specification. The specification at Figure 2 provides a list of the different cis element with the corresponding transcription factor and reporter sequence. It is not apparent from the listing the relative amount or combinations of the kind of the different cis and/or reporters comprise in the library. There is no process step as to a library wherein the recognition sequence and/or cis contained therein is varied or to the library of hybridization probes used

in the hybridization assay in the determination of the different varied reporter. Furthermore, the specification fails to identify a single activated transcription factor that forms a complex with the cis/reporter, let alone, the innumerable activated transcription factor (tf) present in a biological cell sample. Neither was there a single biological sample given to show that even a single activated tf has been identified. This is made more compelling because not a single working example has been provided. There are no specific experimental conditions that are described to identify the numerous tfs present in a complex cell sample. As stated by Li et al (US 2002/01686400) at page 8, [0107] ".. it is important to understand that in any library system encoded by oligonucleotide synthesis one cannot have complete control over the codons that will eventually be incorporated into the peptide structure. This is especially true in the case of codons encoding stop signs…" Due to the high level of DNA binding specificity of transcription factors, each transcription factor will typically bind to a different DNA sequence. In some instances, a related family of transcription factors may bind to the same DNA sequence. Selection of the sequences used in the hybridization probes may be based on the different tfs that one wishes to detect in a sample. This in turn may depend on the type of organism, cell, or disease state

one wished to identify and/or monitor the gene expression of. See University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003).

The specification fails to teach how to use and making a library of cells that comprises 100 different cis elements and/or a reporter sequence with 2000 bases in length. See University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003).

Applicants have not responded to this rejection. Since applicants did not respond to this rejection, it is believed that applicants are acquiescing therewith.

Claims 1-19, 21-24 and 29-31, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The as-filed specification does not provide support for the presently amended claim 1. For example, the specification does not support the claimed wherein "each cis element sequence corresponds to…"; "expressing the library of construct in transfected or transduced cell sample to form…"; "identifying

the cis elements that correspond to their respective reporter sequences encoding the mRNA transcription products..." MPEP 714.02 clearly states that applicants should point out where in the specification support for the newly added limitations exist.

***Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19, 21-24 and 29-31, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In view of the amendments to the claims and cancellation of claim 20, 35 USC 112, second paragraph rejection in the last Office action is withdrawn. However, the claims, as amended are rejected as follows:

Claim 1 is confusing as it is incomplete in omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. It is not clear as to how the library of molecules in a cell sample is expressed. Also, it is not clear as to the formation of mRNA transcription products

from said expressing step. [Note the whole step of expressing is confusing, especially in the absence of positive support in the as-filed specification]. Furthermore, is the claimed reporter sequence encodes a transcription product?

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-19, 21-24 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb (6,579,675) in view of Mauro et al (WO 01/55371) and Kauffman et al (6,413, 723) for the reasons set forth in the last Office action.

***Response to Arguments***

Applicants argue that the expression library in Kamb does NOT contain a reporter gene. Instead, it is the host cell into which the expression vector is introduced that contains a reporter gene under the control of a cis regulatory sequence. Thus, Kamb fails to teach the claimed method wherein a library

of constructs each comprising a cis element and a reporter sequence is introduced to a cell sample.

In reply, applicants' broad claim does not differentiate from Kamb's library containing a host cell and then introduced into a cell sample. It is not apparent from the claims or specification just how the library construct is constructed. Are the components of the library directly transfected into a cell sample i.e., without any vector or host cell to express the library to enable binding to transcription factors in a complex sample cell? The method of Kamb presents detail steps which appear to be lacking in the broad claimed method. Kamb constructs a library in a vector, transfect said vector into a host cell relative to a vector containing cis and reporter gene such that the cis is expressed by the host cell. The expressed cis with the reporter is then introduced into a sample cell that binds to multiple transcription factors in the sample. Thus, Kamb renders obvious the broad claimed method prima facie obvious.

Applicants argue that neither Mauro et al. nor Kauffman teaches or suggests the claimed method. Mauro et al is argued to teach a method of identifying oligonucleotides having transcriptional or translational activity, not transcription factors (which are proteins). But acknowledge that to

do so, a random synthetic oligonucleotide sequence that is based on, but different from a known oligonucleotide such as a known transcriptional regulatory element, is incorporated into an expression vector. Page 5, lines 18-22. Thus, Mauro et al is argued, fails to teach the claimed method of identifying multiple transcription factors by using a construct comprising a cis element that is known to bind to a transcription factor, such as the one listed in the table shown in Figure 2.

In reply, applicants' arguments are not commensurate in scope with the claims. The cis element in Figure 2 is not a limitation present in the claims. Furthermore, a random sequence does not imply that it is not a known sequence. Rather, a known sequence in which a part is randomized. Thus, Mauro discloses a known transcriptional regulatory element except randomized.

It is argued that Kaufmann merely discloses a random population of oligonucleotides of low diversity, which, similar to Mauro, fails to teach the claimed method.

In response, obviousness does not require that prior art show a high diversity, especially since the claim does not recite a high diversity population of oligonucleotides. In considering disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also inferences which one skilled in the art would reasonably be

expected to draw therefrom. In re Preda, 159 USPQ 342; In re DeLise 160 USPQ 806. Accordingly, the combined teachings of the art render the claimed prima facie obvious.

Claims 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb in view of Mauro as applied to claims 1, 6, 12, 18-19, 24 and 29 above, and further in view of Weismann et al (6,066,452) for reasons of record.

***Response to Arguments***

It is argued that Weissman et al discloses a method for identifying new pairs of transcription factor-DNA binding sites by using a library of nucleic acid probes with randomized sequences. Column 2, lines 4-15. Specifically, Weissman et al. teaches using a library of oligonucleotide probes having randomized sequences to "fish out" transcription factors that can bind to any of the randomized DNA sequences (column 13, Table 3). Thus, Weissman also not only fails to teach the claimed method of introducing to a cell sample a library of constructs each comprising a different cis element known to bind a transcription factor, a promoter and a reporter gene, but also fails to teach expressing the reporter sequence and isolating the mRNA products as specified in claim 1.

In response, applicants' arguments as to the new pairs transcription factors identified by Weissman is unclear. Are the

transcription factors, as claimed being identified already a known pair in an unknown cell sample? Furthermore, Weismann is employed for the purpose of teaching an array, not for the purpose as argued. Kamb teaches all the argued method steps not shown by Weismann, except for an array. Accordingly, the combined teachings of Weismman using an array in the method of Kamb are prima facie obvious to one having ordinary skill in the art.

No claim is allowed.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will

expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains claims 25-28 and 47-50 are drawn to a nonelected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571)272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-7924 for regular communications and (703) 308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
January 24, 2005